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Filed : June 27, 2003

#### REMARKS

Claims 85-92, 107-115 are currently pending. Claims 85, 90, 107, 109, 110, and 111 have been amended. New Claims 112-115 have been added. Support for the amended and new claims can be found throughout the specification, the original claims, and the figures. For example, paragraphs 0139 and 0032 note that a computer system can be employed for performing, storing, manipulating and presenting (implicitly to a user) the products of the methods disclosed. Similarly original Claims 11, 12, 41, 42, and 79-84 disclose computer based devices that can be used for implementing the methods. Paragraphs 0110 and 0111 disclose one embodiment of outputting various results. Support for the various particular methods now recited in some of the claims can be found, for example, in the original claims (e.g., Claim 8) and in paragraphs 0055-0060, 0062, and 0140-0148 and FIGs. 2 and 3. All paragraph numbers are in reference to the online version of the published application.

#### *Objection to specification:*

The Examiner has objected to the use of embedded hyperlinks. The website addresses have been removed by the present amendments. Applicants request that the objection be withdrawn.

#### *Claims 85 and 107-111 are adequately described in the original specification.*

The Examiner has rejected Claims 85 and 107-111 as allegedly including elements that are not supported by the originally filed claims or disclosure. The Examiner appears to have found that, in the Response filed 11/13/2006, no support was provided in regard to the element of "a second predictive method further comprising the step of comparing the candidate peptide sequence data to the sequence data of the peptide of known affinity." Applicants respectfully traverse. While Applicants believe that sufficient support was provided in the previous Response, Applicants submit the present additional comments.

The concept of having a first and second method for predicting affinity is clearly disclosed in original Claim 1, which recites:

1. A method for predicting the binding affinity of a peptide for a MHC protein, comprising providing a prediction of binding affinity by two or more methods, and then combining the predictions of those methods.

Similarly, original Claim 18 recites:

18. A method for evaluating the affinity of a candidate peptide for a protein, consisting of: obtaining sequence and binding affinity information for a set of known peptides; obtaining sequence data for a candidate peptide; generating a first evaluation of affinity of said candidate peptide for said protein by comparing the sequence of said candidate peptide with data developed from said information for a set of known peptides with a first prediction method; generating one or more additional evaluations of affinity of said candidate peptide for said protein using said information for a set of known peptides and one or more additional prediction methods different from said first method used to generate said first evaluation of affinity; and combining said first evaluation and said one or more additional evaluations into a combined evaluation.

While Claim 18 refers to the comparison of sequence data as the “first” evaluation, and then refers to a later second evaluation, one of skill in the art will recognize that the present adjustment in terminology is merely one of form and not substance and the previous amendments are clearly supported by the original claims. Moreover, Figures 1 and 2 clearly denote using at least two methods for predicting binding affinity. In Figure 1, one prediction of binding affinity is generated by using individual algorithmic analysis of known peptide information and candidate peptide sequence information. Figure 2 clearly depicts combining two methods (a first and a second) as recited. Further support for these concepts can be found in paragraphs 0013, 0028, 0030, and 0060 (of the online version of the published application).

As such, the previous amendment was fully supported by the specification. Applicants request that the rejection be withdrawn and the claims allowed.

*Claims 85-92 and 107-111 are drawn to statutory subject matter.*

The Examiner has asserted that Claims 85-92 and 107-111 are drawn to non-statutory subject matter. In particular, the Examiner has asserted that the results from the methods are not tangible because they are not “communicated to a user” or involve some other “physical transformation.” Applicants respectfully submit that these options are not requirements for establishing that the claimed subject matter is statutory. However, in the interest of accelerating prosecution on the merits, Applicants have amended the claims to now recite that a result is outputted, as suggested by the Examiner on page 4 of the Office Action or to indicate that at least

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certain steps are performed on a computer (and therefore clearly result in a physical transformation. Applicants request that the rejection be withdrawn and the claims allowed.

*Claims 85-92 are enabled.*

The Examiner rejected Claims 85-92 under 35 U.S.C. §112, first paragraph for lack of enablement. The Examiner asserted that an undue amount of experimentation would be required to make and use the claimed invention. In making the rejection, the Examiner noted that “[b]oth structure-based and sequence-based methods for assessing the binding affinity between candidate peptides and target proteins are well known in the art.” (Office Action, p. 6). The Examiner further noted that the instant claims do not recite such an element.

Claims 85 and 90, from which the other rejected claims depend, have been amended to recite the aspects acknowledged by the Examiner to be well known in the art (structure-based and profile-based techniques). In addition, LP and QP options have also been added to the list of possible methods. Applicants note that the example and the present disclosure employs profile-based techniques, LP, and QP techniques (see, e.g., 0140 to 0151). Furthermore, the specification has a detailed description of exemplary techniques (e.g., LP, 0074-0077; QP, 0063-0069; and profile based, 0078-0091). Additionally, further descriptions of such techniques can be found in paragraphs 0041-0059. Thus, in light of the extensive and detailed discussion, the example, the state of the art (which the Examiner acknowledges to be high/well known) and the present amendments, Applicants submit that the present claims are enabled. Applicants request that the rejection be withdrawn and the claims allowed.

*Claims 85-89, 107, and 108 are sufficiently definite.*

The Examiner has rejected Claims 85-89 as being indefinite because the phrase “the binding affinity” lacks antecedent basis. Applicants thank the Examiner for noting this and have amended the claim appropriately. Applicants request that the rejection be withdrawn and the claims allowed.

The Examiner has rejected Claims 107 and 108 as allegedly being unclear in regard to how the “similarity” is used to predict the second binding affinity of the peptide of known

affinity. Applicants respectfully note that the claim does not recite that the binding affinity of the peptide of known affinity is being predicted. The relevant section of Claim 107 recites:

predicting a second binding affinity for the candidate epitope for said MHC protein by using a second predictive method, wherein said prediction comprises a comparison between the sequence data for the at least one epitope of known affinity and the sequence data for the candidate epitope in order to determine a similarity, and then using the similarity between the two sequences to predict the second binding affinity based upon the affinity of the peptide of known affinity...

As is clear from the claim, the binding affinity of the peptide that has a known affinity is being used for the second prediction. Additionally, the second prediction is for the candidate epitope, not the peptide of known affinity. Applicants respectfully submit that this is clear from the current claim language and request that the rejection be withdrawn and the claim allowed.

*Claims 85, 87-90, and 92 are novel over Yaffe et al.*

The Examiner asserted that Claims 85, 87-90, and 92 are anticipated by Yaffe et al. The Examiner found that Yaffe teaches, among other aspects, a profile-based scoring algorithm comprising bit scores calculated using a first equation. The Examiner has asserted that the bit scores are a “first affinity” and the first equation is a “first predictive method.” Similarly, the Examiner has asserted that the profile-based scoring algorithm of Yaffe also comprises a raw sequence score (which the Examiner has asserted is a second affinity) that is calculated using a second equation (which the Examiner has asserted is a “second predictive method”). The Examiner also found that the normalization of the above scores is the same as scoring the presently recited binding affinities. Applicants respectfully traverse.

As an initial point, Applicants note that no evidence or reasoning has been provided to demonstrate why the “scores” taught in Yaffe would or could be considered to be affinities of a candidate peptide for a target epitope. It appears that the Examiner is asserting that the terms are interchangeable; however, the Examiner has not explained how or why he considers this to be the case. Applicants note that this does not appear to be the case given the actual teachings in Yaffe. It is clear that Yaffe defines the bit scores as being “derived for each position.” (page 349, col. 1, emphasis added). Thus, these scores are determined for specific amino acid positions, and not for the binding ability of candidate peptide to bind to the target protein (as explicitly recited in

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the claims). As such, these scores do not qualify as binding affinities for the candidate peptide for the target protein.

Moreover, it is clear from the disclosure on page 349 of Yaffe that the two scores are not normalized and then combined. Rather, the "raw score" is a function of the "bit score" (first paragraph, first column, page 349). There is no teaching or suggestion that these two scores can be normalized and then combined together, as they are acted upon serially.

Finally, Applicants note that Claims 85 and 90 recite using two different methods and further have now been amended to recite that each of the two methods are selected from a profile-based, LP, QP, anchor scoring, and/or a structure-based method. At best, Yaffe teaches one profile based method and does not teach combining two of the above techniques that are different. As such, Yaffe does not anticipate the presently claimed method.

In view of the above, Applicants request that the rejection be withdrawn and the claims allowed.

*Claims 85, 86, 90, 91, 107, 109-111 are novel over Mamitsuka.*

Claims 85, 86, 90, 91, 107, and 109-111 have been rejected by the Examiner as anticipated by Mamitsuka. The Examiner has asserted that Mamitsuka teaches, among other aspects, determining a forward probability score (which the Examiner asserts is a first affinity) using a HMM (which the Examiner asserts is a first predictive method), determining a backward probability score (which the Examiner asserts is a second affinity), using a different HMM (which the Examiner asserts is a second predictive method), and combining the forward and backward probabilities. Applicants respectfully traverse the rejection.

As an initial point, Applicants note that the Examiner has provided no evidence or reasoning for why the "forward probability score" or the "backward probability score" would or could be considered the same as a first and second affinity. Applicants fail to see how the asserted "forward" and "reverse" probability scores (which describe transition probabilities between states) are the same as the affinity that is described in the specification and recited in the claims.

Furthermore, in making the rejection the Examiner has asserted that two different HMM techniques are being used, each one qualifying as a different predictive method that

independently provides a first and second affinity. Applicants do not agree with the Examiner's characterization of the art. Rather, it appears that the forward and backward probabilities are part of a single HMM in Mamisuka. In particular, Mamisuka explicitly defines the forward probability as "the probability that the model generates the first  $t$  symbols of the input sequence  $O^s$  and arrives at state  $j$ ", while the backward probability is "the probability that the model will generate the rest (all but the first  $t$  symbols) of the input sequence  $O^s$  given that it is now at state  $j$ ." (end of col 2, page 462 and start of col 1, page 463). Applicants fail to see how these forward and backward probabilities, given their explicit definitions in Mamisuka, are relevant to the present claims that involve different predictive methods for predicting affinities. The values calculated in Mamisuka merely relate to the probability of the transition occurring either to or away from  $t$ , and do not appear to, independently, be a method of predicting a first and then a second affinity. Thus, these aspects do not appear to teach the recited elements either. If the rejection is to be maintained, Applicants respectfully request that the Examiner provide some reason for equating the two.

Finally, Applicants note that Claims 85, 90, 112 and their dependent claims are now explicitly directed to the combination of different recited methods, some of which involve profile/motif analysis, structural-based techniques, LP, anchor scoring, and/or QP based methods. For these claims, it is very clear that Mamitsuka does not teach such a recited combined method involving at least two of the above techniques.

Applicants respectfully submit that Mamitsuka does not anticipate the claims and respectfully requests that the rejections be withdrawn and the Claims allowed.

While the elements in the independent claims have been discussed in detail above and are believed to be sufficient to overcome the above reasons for rejection; Applicants note that the dependent claims recite additional elements that further distinguish the claimed invention over the cited art.

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New Claims

New Claims 112-115 include similar elements to those noted above in regard to the statutory subject matter, enablement, and anticipation rejections. As such, these claims should also be allowable for the reasons noted above.

CONCLUSION


In view of the foregoing amendments and remarks, Applicants respectfully submit that the pending claims are in condition for allowance and request the same. If, however, some issue remains that the Examiner feels can be addressed by Examiner Amendment, the Examiner is cordially invited to call the undersigned for authorization.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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